THIAZIDES AND DIABETES MELLITUS

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THIAZIDES are widely used either alone as diuretics in cardiac failure, or in combination with other drugs as a means of reducing high blood pressure. *Medindex* (April–June, 1965) lists no less than sixteen thiazide preparations and nine hypotensive agents containing thiazide as an important constituent. Manufacturers' leaflets to the medical profession vary enormously in their advice and precautions in relation to their side-effect on carbohydrate metabolism. Many fail entirely to mention this important and frequent complication; others quote glycosuria, decrease in glucose tolerance or a frank warning that diabetes can be precipitated or made worse if already present. None give any idea of the frequency of thiazide-induced diabetes.

Four well-known textbooks of medicine (1964 editions) do not mention this possible hazard and though precautionary advice appeared in *Prescribers' Journal*[1] and *The Practitioner*[2], neither give any indication how often one might expect to meet this danger in practice.

Experimentally, Shapiro, Benedek and Small,[3] showed that of 15 hypertensive 'potentially' diabetic patients with blood sugars 180 mg. per cent or more after glucose loading, 13 showed impaired carbohydrate metabolism after administration of chlorothiazide and of these 13, five developed symptomatic diabetes. Two other patients not considered potentially diabetic, similarly showed impaired carbohydrate metabolism after chlorothiazides. They conclude that thiazides should not be used to treat benign non-progressive hypertensives as they are capable of inducing disturbance of carbohydrate metabolism which may terminate as diabetes mellitus.

Survey of frequency in general practice

In November, 1965, case 1 of series 1 was discovered and a scrutiny was made of my own and two of my partners' practices representing a list of approximately 10,000, and eight further cases were discovered (table I).

All these patients are either 10 or 20 per cent overweight or where

it has been difficult to get an exact weight due to their clinical condition, described as grossly overweight. Diabetes mellitus has been confirmed by fasting blood sugar levels or glucose tolerance curves in all but one, J.D. aged 84, where repeated urine sugars exceeded two per cent until brought under control by treatment.

TABLE I

DETAILS OF THE NINE CASES IN THE FIRST SERIES

Number	*Sex*	*Age*	*Drug*	*Starting date of drug*	*Date of discovery diabetes*	*Interval between thiazides and diabetes*
1 A.M.	F	51	Reserpine and bendrofluazide	20/ 4/64	17/11/64	7 months
2 M.B.	F	64	,,	27/ 3/64	21/ 1/65	9 ,,
3 R.S.	M	68	,,	13/ 2/63	24/ 9/63	7½ ,,
4 A.T.	F	64	,,	19/10/64	25/ 1/65	2½ ,,
5 D.S.	M	65	,,	24/ 1/61	28/ 2/64	37 ,,
6 M.A.	F	72	,,	1/ 3/64	10/ 5/65	16½ ,,
7 J.D.	M	84	Resperine c hydrochlorozide and potassium chloride	15/ 1/59	12/ 1/65	59 ,,
8 M.V.	F	66	,,	12/ 2/62	Previously known 'mild diabetic' controlled by diet alone—by 4/10/63 required amputation for diabetic gangrene and has diabetic retinitis	
9 B.D.	F	77	,,	28/10/60	31/ 3/65	55 months

Case 1 has a son who developed diabetes mellitus in childhood and cases 1 to 7 and 9 may well have been 'pre-diabetic' which would have been revealed by cortisone or prednisolone glucose tolerance tests. Case 8 appears to be a classical example of mild diabetes readily controlled by diet until thiazides made her condition deteriorate. A second example of this is known, but is not quoted as the patient is now deceased and there are no detailed records. Nine others in this age range, similarly not less than ten per cent overweight and taking thiazides for equivalent periods, have been checked and, to date, have developed no evidence of diabetes.

The morbidity rate, ignoring case 7 which has not been confirmed by blood sugar, is, therefore, one per 1,250 patients and, if this is representative of the country as a whole, means that all doctors in general practice have 1, 2 or 3 diabetic patients suspiciously attributable to or made worse by thiazides.

Survey in hospital inpatients

In April 1965, permission was obtained from the medical superintendent to scrutinize all diabetic patients and their records in the wards of Lancaster Moor Hospital. These patients are subjected to an annual physical examination including urine checks and, therefore, the possibility of diabetes going undetected or being undetected until thiazides made it worse is less likely than in a busy general practice.

Seventy-eight patients with diabetes were surveyed. In all cases diabetes has been confirmed by a glucose tolerance curve.

Two of the 78 have apparently been induced by thiazides, two

TABLE II

DETAILS OF CASES UNDER TREATMENT IN LONG STAY HOSPITAL

Number	*Sex*	*Age*	*Drug*	*Starting date of drug*	*Date of discovery diabetes*	*Interval between thiazides and diabetes*
1 J.B.	F	80	Polythiazide potassium chloride	30/12/64	12/ 2/65	1½ months
2 T.S.	M	44	Hydrochlorozide	24/10/62	3/ 7/63	8 „
3 M.R.	F	66	Hydrochlorozide and potassium chloride	23/ 3/61	7/11/56 (onset)	Daily insulin increase from 10 to 50 units
					1/ 9/61 (deterioration started)	4 months
4 B.N.	F	71	Chlorothalidone	15/ 7/64	8/ 3/60 (onset) 19/11/64 (deteriorated 2 months)	Daily insulin regime increased after 2 months
5 N.N.	F	44	Bendrofluazide ..	20/ 1/65	18/ 5/47	No apparent deterioration
6 B.G.	F	71	„ ..	29/ 1/65	6/ 2/63	„
7 A.W.	F	86	„ ..	22/ 4/65	19/ 7/58	„
8 A.H.	F	78	Polythiazide ..	2/ 9/63 (5 days only)	1953 high blood sugar curve	
9 to 78		25 to 92	None		13 onset prior to 1957 when thiazides introduced 4 onset prior admission dates doubtful 53 onset after thiazides introduced but no history of thiazide therapy	

have shown appreciable deterioration after administration of thiazides, i.e., a rate of 2.4 per cent in each category. One has shown a similar deterioration after chlorothalidone, a member of the newer non-thiazide diuretics, and a warning that diabetes can be induced is mentioned in the manufacturers' literature. Chlorothalidone, quinethazine, frusemide and chlorexoline all contain the same sulphamoyl-benzine grouping, and, likewise to the thiazides, are apparently antidiuretic in diabetes insipidus. Series 2, case 4, suggests at least one of this group may have similar diabetogenic properties to the thiazides—this frequency as yet to be determined.

Cessation of thiazides

Table III illustrates some results obtained when thiazide administration was withdrawn. The case numbers correspond with series 1 (table 1).

Case 1 has a son with diabetes and it seems that thiazides have precipitated irreversible though easily controlled diabetes. Cases

TABLE III

RESULT OF WITHDRAWING DIURETICS FROM PATIENTS LISTED IN TABLE I

Number	*Sex*	*Age*	*Duration drug before discovery*	*Hypotensives*	*Fasting blood sugar*	*Diabetic therapy*
1 A.M.	F	51	7 months	Reserpine c bendrofluazide	185	Diet only
2 M.B.	F	64	9 ,,	,,	160	Diet and tolbutamide 6 x 0.5 g.
3 R.S.	M	68	7½ ,,	,,	155	Diet and tolbutamide 2 x 0.5 g.
5 D.S.	M	65	37 ,,	,,	235	Diet and 500 mg. Chlopropamide
9 B.D.	F	77	53 ,,	Resperine hydrochlorthiazide c potassium chloride	480	Diet and 2 x 0.5 g. tolbutamide
				EX-THIAZIDES		
1 A.M.	F	51		Methyl dopa ..	200	Diet only
2 M.B.	F	64		,,	83	,,
3 R.S.	M	68		,,	80	,,
5 D.S.	M	65		,,	85	,,
9 B.D.	F	77		Methyl dopa and frusemide 40 mg. 5 days 1 week	113	,,

2, 3, 5 and 9 show a return to normal carbohydrate metabolism and this occurred in all cases within two to three weeks. The results are equally good irrespective of the duration of thiazide therapy. Case 9 was originally one of the controls for Series 1 and checked as symptom free with no glycosuria, but she subsequently developed two per cent sugar in her urine; consequently any further checking has included an immediate blood sugar estimation by " Dextrostix ". This was the only case in which continuous diuretics were considered essential because of incipient cardiac failure. Frusemide was the diuretic of choice because of previous favourable reports in diabetes.

Frusemide

Schaefer[4] reports that of 59 diabetics, 33 became decompensated in their diabetic regime after thiazide treatment but were readily re-stabilized one to four weeks after cessation of the thiazide therapy. He further showed that of the 33 initially decompensated 19 were unaffected by frusemide. Three of the remaining 26 were unaffected by frusemide, and another 21 of a different series were likewise unaffected by frusemide. Other investigators[5, 6, 7] have similarly found frusemide free from diabetogenic properties in their series.

Conclusions

Thiazide-induced diabetes is frequently met with in overweight individuals and this may not become clinically obvious until some considerable time has elapsed. The frequency is such that the treatment of all diabetics is worth reviewing to exclude thiazide effects which may be making stabilization of their condition more difficult.

The theory that thiazides in some way interfere with insulin carriage is supported by the rapid improvement which can occur when thiazides are stopped even when they have been in use for some considerable time, and by the decompensation which appears if thiazides are given to an already diabetic patient.

Frusemide initially seems a safe diuretic in respect to carbohydrate metabolism, but in view of the experience with thiazides and their sometimes long delayed action, further observations with its continued use is advisable.

Acknowledgements

I wish to thank Dr W. J. Hay, consultant physician, and Dr S. Smith, consultant psychiatrist, for their help and advice with this paper; also Mr H. L. Lewty, chief pharmacist to the Lancaster Moor Hospital.

REFERENCES

Wilson, G. M. (1961). *Prescribers' Journal*, **1**, p. 55.
Heller, H. (1965). *The Practitioner*, **194**, p. 59.
Shapiro, A. P., Benedek, T. G., and Small, J. L. (1961). *New Engl. J. Med.*, 265, requoted*Modern Medicine* (1962), **7**, No. 7.

Schaefer, H. F. (1964). *Die Med. Welt.*, **16**, 922.
Bencomo, L., Fyvolent, J., Kahana, S., Kahana, L. (1965). *Current Therapeutic Research*, **7**, No. 6.
Verel, D., Stentiford, N. H., Rahman, F., Sayner, R. (1964). *Lancet*, **2**, 1088.
Robson, A. O., Kerr, D. N. S., Ashcroft, R., Teasdale, G. (1964), *Lancet*, **2**, 2085.

Canadian medical students' judgements of the prestige ascribed by the public to various fields of medical practice. D. G. FISH and JOHN H. MOUNT. *Journal* College of General Practice of Canada. 1966, **12**, 27.

This is a pilot study of the judgements made by a sample of Canadian medical students of the prestige that is assigned to the various fields of medical practice by the public. Fields which might be anticipated as ranking high in the public's eyes were so judged by the student; for example, surgery and internal medicine. Those fields which are removed from the focus of the public, such as pathology and medical research, were judged as of low prestige value as compared with the fields of clinical practice. General practice held its own with the specialties ranking fourth in overall measurement, but the students displayed considerable variance among themselves with respect to its ranking. Differences between male and female medical students in their respective ranking of the fields were apparent only in the case of neurology and obstetrics. Striking differences between students in the various years of the medical course occurred in the assignment of ascribed prestige to psychiatry, neurology, and internal medicine. Psychiatry falls steadily in ascribed prestige throughout the four years of the course while internal medicine appears to climb. General practice falls in ascribed prestige during the final year. 'It would appear that the curriculum and exposure to a variety of teachers and settings of medical practice influence the students' views of the fields of medical practice as they progress through medical school'.